EXHIBIT E

Author's Accepted Manuscript

Transvaginal Mesh Placement and the Instructions for Use: A Survey of North American Urologists

Gina Kirkpatrick, DO, Kenneth D. Faber, MD, Debra L. Fromer, MD

PII: S2352-0779(18)30087-6
DOI: 10.1016/j.urpr.2018.05.004
Reference: URPR 349

To appear in: *Urology Practice*
Accepted Date: 1 May 2018

Please cite this article as: Kirkpatrick G, Faber KD, Fromer DL, Transvaginal Mesh Placement and the Instructions for Use: A Survey of North American Urologists, *Urology Practice* (2018), doi: 10.1016/j.urpr.2018.05.004.

The risk information in the Instructions for Use for transvaginal mesh kits for prolapse and incontinence has been one of the key factors in multimillion dollar litigation against the companies manufacturing these kits. But do the implanting physicians read these documents and with what frequency?

Transvaginal Mesh Placement and the Instructions for Use: A Survey of North American Urologists

Gina Kirkpatrick, DO: Florida Hospital Physician Group
Kenneth D Faber, MD: Southern California Permanente Medical Group
Debra L Fromer, MD: Hackensack University Medical Center (Corresponding Author)

Key Words: transvaginal mesh, incontinence, prolapse, midurethral sling

Abstract

Introduction: Since the issue of the FDA Public Health Notification in 2008 regarding complications associated with the use of transvaginal surgical mesh for pelvic organ prolapse and stress urinary incontinence, multimillion dollar litigation has been brought against the companies that have manufactured these products. One component of the litigation has focused on risk information provided in the Instructions for Use (IFU) document provided with each mesh kit. The purpose of this study is to evaluate what type of urologists are utilizing transvaginal mesh kits and their utilization of the IFU provided with each mesh kit.

Methods: A 14-question survey was e-mailed to all urologists registered with seven of the eight geographic sections of the AUA in 2016. The survey inquired about the utilization of transvaginal mesh kits for both prolapse and incontinence, as well as how often, if ever, the urologist has read the IFU.

Results: There were a total of 314 responders. The majority of responders (79.3%) identified as general urologists and 12.7% as FPMRS-trained urologists. Of the responders reporting having placed midurethral slings and/or a mesh prolapse repair kit, 36.9% and 23.1% had never read the IFU, respectively. Of those providers who had read the IFU, the most common frequency was once prior to the first placement.

Conclusions: The pertinent role the IFU plays in mesh related litigation stands in contrast to our finding that many surgeons who utilize these kits infrequently if ever read them.

Introduction

The purpose of this study is to evaluate what type of providers are utilizing transvaginal mesh kits for incontinence and/or prolapse and their utilization of the Instructions for Use (IFU) provided with each mesh kit.

Transvaginal polypropylene mesh for treatment of pelvic organ prolapse was first proposed in 1998 to improve unsatisfactory outcomes after anterior colporrhaphy.[1] Since this time, numerous studies have reported on outcomes of transvaginal mesh placement for prolapse. These include prospective trials with head to head comparisons of mesh placement versus anterior colporrhaphy, often revealing a higher anatomic success rate with mesh.[2-5] A Cochrane meta-analysis of these studies, including 16 randomized controlled trials between 2001 and 2015 with 1,976 women evaluated surgical outcomes for women with anterior compartment prolapse. The meta-analysis predicted that 32% to 45% of women would have recurrent prolapse after native tissue repair, compared to 13% after mesh repair.[6] This success in both anatomic and subjective efficacy outcomes with transvaginal mesh for prolapse repair led to a rapid increase of pelvic organ prolapse surgery amongst urologists.[7]

However, with the introduction of transvaginal mesh for prolapse and the rise in its utilization came complications that were reported as part of device utilization and in 2008 the FDA issued a public health notification regarding what it considered to be rare but serious complications associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress urinary incontinence.[8] In July 2011, the FDA issued an update in which they identified surgical mesh for transvaginal repair of pelvic organ prolapse (POP) as an area of continuing serious concern.[9] Although mesh for the use of stress urinary incontinence (SUI) was subsequently dropped in the update, transvaginal mesh has become a hot topic amongst urologist, gynecologists, patients, and the medico-legal community.[10-17]

Much of the ongoing litigation that has been brought against the companies manufacturing these products has centered on contents of the IFU provided with the mesh kit. The IFU is the document required by the FDA to be inserted into the packaging for every medical device manufactured in the U.S. The IFU includes multiple sections, such as Indications, Contraindications and Instructions. However, in product liability suits, the key claim that the device company failed to warn consumers of the risks of the product focuses on the Adverse Events and Warnings sections of the IFU. The information included in the IFU is designed to be read by the physician, who in this circumstance is considered the "learned intermediary." This term was coined in a 1966 decision by the Eighth Circuit when the court reasoned that "the purchaser's doctor is a learned intermediary between the purchaser and the manufacturer," in this case the purchaser being the patient, and the manufacturer the prescription drug manufacturer. This doctrine also applies to physicians as the learned intermediary between the medical device company and the patient. Decades later and thousands of cases later, the learned intermediary doctrine is recognized in the majority of states.

The legal importance of the IFU with respect to the learned intermediary doctrine in the transvaginal mesh litigation prompted us to evaluate if and with what frequency surgeons who utilize transvaginal mesh for POP and/or SUI read the IFU provided with the kits.

Materials and Methods

We contacted the geographic sections of the AUA in 2015, which together represent the majority of North America, asking for their assistance with our study. Seven of the eight geographic sections of the AUA agreed to participate. The New England section of the AUA did not agree to participate. Each geographic section sent an email to all members of the section that explained the purpose of the study and provided a link to an online site if the individual agreed to participate. The survey, which can be seen in Table 1, is comprised of 14 questions which assess each responder's utilization of transvaginal mesh, both for SUI as well as prolapse, during his or her career as well as in the past year. There are more specific questions regarding the types of mesh kits the provider has utilized. It also asks whether the responder has read the Instructions for Use provided with the kits, and if so, with what frequency. No names or other identifying characteristics were asked. All responses were recorded and tabulated by an online website, surveymonkey.com.

Results

A total of 7,212 surveys were sent to active members of seven of the eight geographic sections of the AUA, with 314 responders for a response rate of 4.7%. Three hundred-thirteen of the 314 responders identified themselves as urologists, while the other identified as an FPMRS Urogynecologist. The majority of responders, 79.3%, identified as general urologists, with 12.7% being FPMRS trained urologists. The remaining 7.6% identified as "other urologist," and may represent urologists still in training.

Nearly 30% of responders had placed over 200 midurethral slings in their career, with only 8.6% stating they had never performed th e surgery. However, 20.8% of responders had not placed a midurethral sling in the prior year, with those who have performing between 1-10 or 10-50. Of the various approaches for midurethral sling placement, the transobturator technique was the most common (29.1%), however the majority of responders had used more than one type (37.4%). The out-to-in approach was more common for both retropubic and transobturator types.

Of 312 responders, 42.0% stated that they had never read the IFU for any midurethral sling. However, as 27 responders (8.6%) have never placed a sling and only 2 omitted the question, it can be assumed that the remaining 25 responders who had not placed a sling can be removed from the data group. Of the remaining 287 responders, 106 (36.9%) had never read the IFU for any midurethral sling.

Far fewer transvaginal mesh kits were utilized for prolapse as compared to incontinence. Over half (55.2%) of responders had never utilized a mesh kit for prolapse, and 79.2% had not performed any in the year prior. Similar to responses regarding midurethral slings, 64.4% of responders report they had never read the IFU prior to mesh placement for prolapse. Using the same logic as above for midurethral sling, 171 responders had never used mesh for prolapse, which leaves 33 of 143 responders (23.1%) who had never read an IFU of a mesh prolapse repair kit.

For providers who reported they have read the IFU for either SUI or prolapse repair with mesh, the most common frequency was once prior to first placement, as seen in Figure 1. Among those who reported reading the IFU until comfortable, all answered they were comfortable before 20 uses, with the majority being comfortable within the first 10 (Figure 2).

Discussion

The management of pelvic organ prolapse has evolved over the last two decades. The prevalence of reoperation after primary pelvic reconstructive surgery was reported as high as 50 to 60% in some studies, [18] prompting the development of a more permanent solution. This led to the advent of polypropylene mesh for transvaginal prolapse repair, which was believed to have a higher efficacy than a standard native tissue repair.[19] However, recent reviews have questioned whether mesh repairs are truly superior to native tissue repairs.[20] Complications such as exposure/erosion in mesh repair have caused some to question the utilization of mesh for prolapse repair, and these complications along with the associated litigation appears to have caused another shift in POP management. [21]

Our results suggest a shift in management away from the utilization of transvaginal mesh, particularly for prolapse repair. Of our responders, 55.2% reported that they have never used mesh for pelvic organ prolapse, however 79.2% state they have not performed any in the last year. Viewed another way, over half of the responders who performed a prolapse repair with mesh in the past have not done so in at least a year. A similar shift is identified with transvaginal mesh use for SUI, with 8.6% of surgeons having never performed the procedure, with that number increasing to 20.8% in the prior year. Although there could be a multitude of reasons for this, the concern regarding mesh complications and litigation is most certainly a factor. Patient reluctance to have mesh-related surgery is also a likely contributing factor, as many patients have seen or heard the advertisements regarding litigation.

Unger noted there was a decline in the use of transvaginal mesh from approximately 70,000 implants in 2010 to 30,000 in 2012.[22] This trend identifying a decline in transvaginal mesh utilization is interesting, one that warrants further exploration. The other purpose of our survey was to identify with what prevalence providers were utilizing the IFU provided with the mesh kits. When excluding those who have never performed the procedure, 36.9% of responders have never read an IFU for SUI sling placement, and 23.1% for POP mesh placement. Some of these individuals may be fellowship trained, however only 12.7% of responders reported being FPMRS trained, and many may have read the IFU. For those responders who have read the IFU, this was most commonly done once prior to first placement, and hence not always read when new products were utilized.

Our results illustrate an important point regarding transvaginal mesh placement and the litigation that surrounds it. In one example of many, a 2014 trial in Dallas involving Johnson & Johnson's Ethicon decision for the plaintiff, the plaintiff claims that after implantation of a TVT-O she experienced pelvic pain and dyspareunia. Her lawyer claimed that the IFU was not adequate and that physicians rely on them to make decisions.[23] However, as evidenced by our results, the information provided in the IFU would not have reached 36.9% of surgeons who have performed a midurethral sling and have never read

the IFU. This would suggest the IFU is neither a decisive factor in the decision-making process regarding mesh implantation nor the sole tool for conveying risks and warnings for many surgeons.

Determining whether or not a physician has read the IFU has been an important point of distinction in some litigation. In a 2013 trial originating in Mississippi brought against Bard for its Avaulta Plus product, one of the plaintiff's claims was the company's failure to warn regarding potential complications of the use of its product. However, the physician stated that he had not read the IFU and hence the summary judgment indicated that no amount of warning in the IFU would have prevented the plaintiff's outcome, as the physician did not read it.[24]

A weakness of this study was the low response rate. It is likely that those not familiar with pelvic reconstructive surgery may not have replied. Additional selection bias may actually favored those who have actually read the IFU. This may have resulted in a falsely elevated number of surgeons reading the IFU.

The IFU as a pertinent legal warning tool in the ongoing mesh litigation belies the finding that it is not a consistently read document. One can further assume that the document is therefore not regularly relied upon by implanting surgeons. The emphasis placed on the IFU in litigation also seems to obviate the fact that urologists and gynecologists performing these procedures should be adequately trained on placement, efficacy and complications prior to utilization. Further, implanting physicians have the capability to be informed of risks of vaginal mesh surgery through training, review of bountiful and robust medical literature, conferences, and discussions with colleagues. Therefore, given the fact that the IFU is not consistently relied upon by physicians as a source of information regarding the complications associated with these procedures, it seems to be unclear from a medical perspective why the ongoing mesh litigation continues to focus on the IFU and perhaps something that should be further addressed in the medicolegal arena.

Conclusion

The advent of transvaginal mesh for POP and SUI has influenced two paradigm shifts in pelvic floor management. The first being the rise in POP surgery as more surgeons utilized mesh kits. The second is the current apparent decline in the use of mesh in transvaginal surgery, a result of the concern regarding their complications and subsequent litigation. The pertinent role the IFU plays in mesh related litigation belies our finding that many surgeons who utilize these kits infrequently, if ever, read them.

References

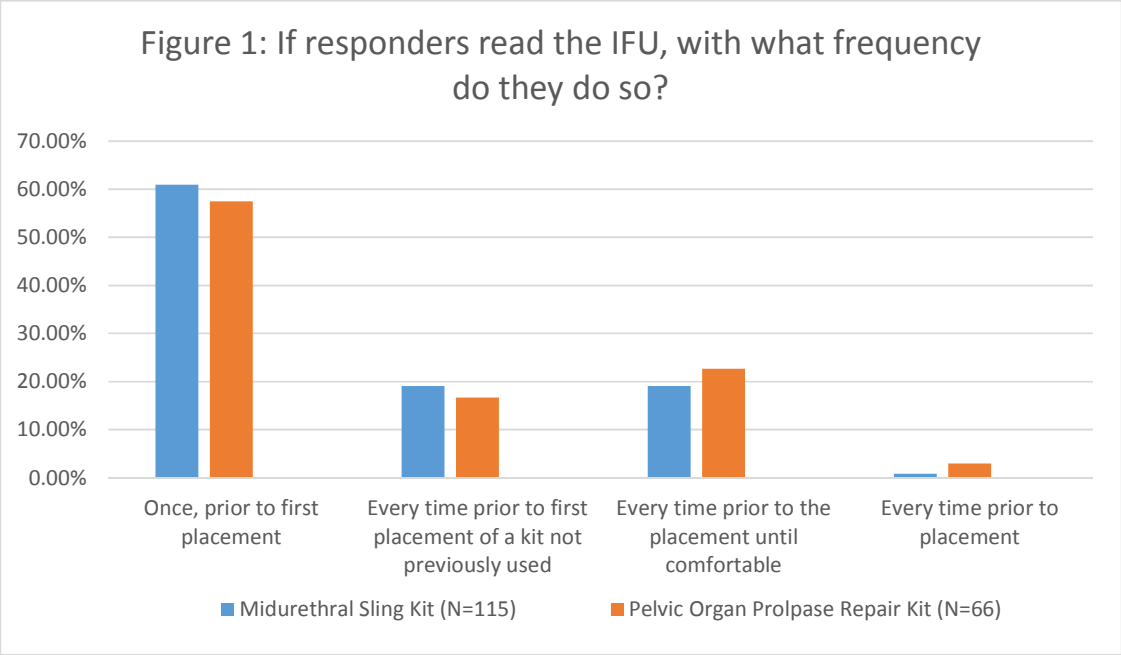
1. A New operation for genitourinary prolapse, Nicita G. Journal of Urology, Sep 1998; Vol 160: 741-745.
2. Primary surgical repair of anterior vaginal prolapse: a randomized trial comparing anatomical and functional outcome between colporrhaphy and trocar-guided transobturator anterior mesh, Vollebregt A, et al. British Journal of Gynecology, Aug 2011; Vol 118: 1518-1527.

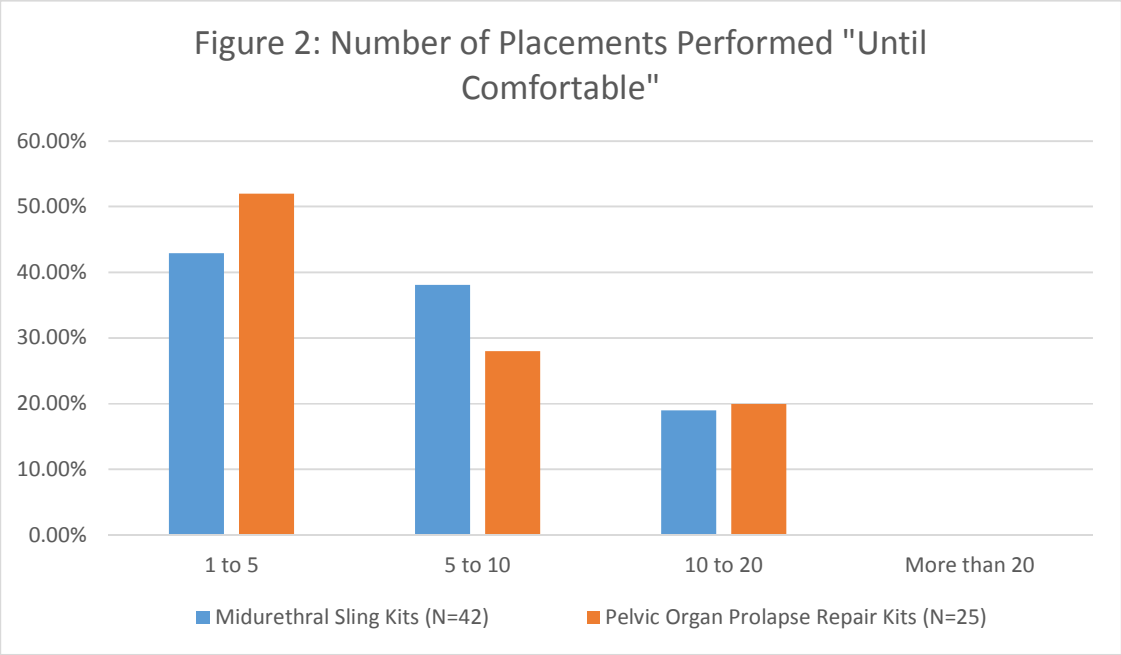
3. The use of transvaginal synthetic mesh for anterior vaginal wall prolapse repair: a randomized controlled trial, Delroy CA, et al. Int Urogynecol Journal, Nov 2013; Vol 24: 1899-1907.
4. Comparison between trans-obturator trans-vaginal mesh and traditional anterior colporrhaphy in the treatment of anterior vaginal wall prolapse: results of a French RCT, de Tayrac R, et al. Int Urogynecol Journal, Oct 2013; Vol 24: 1651-1661.
5. Colporrhaphy compared with mesh or graft-reinforced vaginal paravaginal repair for anterior vaginal wall prolapse: a randomized controlled trial, Menefee SA, et al. Obstetric Gynecology, Dec 2011; Vol 118: 1337-1344.
6. Surgery for women with anterior compartment prolapse (Review), Feiner et al. Cochrane Database of Systematic Reviews, 2016, Issue 11. Art. No.:CD004014. DOI: 10.1002/14651858.CD004014.pub6.
7. Changes in pelvic organ prolapse surgery in the last decade among United States urologists, Elterman DS, et al. Journal of Urology, Apr 2014; Vol 191: 1022-1027.
8. Public Health Notification: serious complications associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress urinary incontinence, US Food and Drug Administration. Oct 2008; http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm
9. UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse: FDA Safety Communication, US Food and Drug Administration. July 2011; http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm
10. Medicolegal issues surrounding devices and mesh for surgical treatment of prolapse and incontinence, Nostia PA, Iglesia CB. Clinical Obstetric Gynecology, June 2013; Vol 5: 221-228.
11. Transvaginal mesh kits –how "serious" are the complications and are they reversible? Lee D, et al. Urology, Jan 2013; Vol 81: 43-48.
12. Complications of vaginal mesh surgery, Chermansky CJ, Winters JC. Current Opinion in Urology, July 2012; Vol 22: 287-291.
13. Mesh sling in an era of uncertainty: lessons learned and the way forward, Chapple CR, et al. European Urology, Oct 2013; Vol 64: 525-529.
14. Impact of the 2011 FDA transvaginal mesh safety update on AUGS members' use of synthetic mesh and biologic grafts in pelvic reconstructive surgery, Clemons JL. Female Pelvic Medicine and Reconstructive Surgery, Jul-Aug 2013; Vol 19: 191-198.
15. Pelvic mesh complications in women before and after the 2011 FDA public health notification, Rice, NT et al. Female Pelvic Medicine and Reconstructive Surgery, Nov-Dec 2013; Vol 19: 333-338.
16. Use of vaginal mesh in the face of recent FDA warnings and litigation, Mucowski SJ et al. American Journal of Obstetric Gynecology, Aug 2010; Vol 203: 103.e1-4.
17. Informed surgical consent for a mesh/graft-augmented vaginal repair of pelvic organ prolapse. Consensus of the 2nd IUGA Grafts Roundtable: optimizing safety and appropriateness of graft use in transvaginal pelvic reconstructive surgery, Miller D, et al. International Urogynecological Journal, Apr 2012; Vol 23: S33-42
18. To mesh or not to mesh: a review of pelvic organ reconstructive surgery, Dallenbach P. International Journal of Womens Health, Apr 2015; Vol 7: 331-343.

19. Tension-free polypropylene mesh for vaginal repair of anterior vaginal wall prolapse, de Tayrac R, et al. Journal of Reproductive Medicine, Feb 2005; Vol 50:75-80.
20. Traditional native tissue versus mesh-augmented pelvic organ prolapse: providing an accurate interpretation of current literature, Stanford EJ, Cassidenti A, Moen MD. International Urogynecol Journal, Nov 2011, Vol 23:19-28.
21. Complications requiring reoperation following vaginal mesh kit procedures for prolapse, Marguiles RU, et al. American Journal of Obstetric Gynecology, Dec 2008; Vol 199:678e1-4.
22. An Update on the Use of Mesh in Pelvic Reconstructive Surgery, Unger C. Current Obstetrics and Gynecology Reports, 2016, Vol 5:131-138
23. Horton, A, (2014, March) Linda Batiste v Ethicon, Day One Testimony. Retrieved from http://www.meshmedicaldevicenewsdesk.com/linda-batiste-v-ethicon-day-one-of-testimony
24. Jones v C.R. Bard, Inc, (2013, June) Memorandum Opinion and Order MDL # 2187. Retrieved from http://cases.justia.com/federal/district-courts/west-virginia/wvsdce/2:2011cv00114/67580/288/0.pdf?ts=1411585518

Table 1: Survey Questions

Q1	What type of provider are you?
Q2	Approximately how many polypropylene mesh midurethral sling kits have you implanted?
Q3	Approximately how many polypropylene mesh midurethral sling kits have you implanted this past year?
Q4	Approximately how many polypropylene mesh kits for prolapse have you implanted?
Q5	Approximately how many polypropylene mesh kits for prolapse have you implanted this past year?
Q6	What type of polypropylene mesh midurethral sling kits have you utilized?
Q7	If you have utilized a retropubic polypropylene mesh midurethral sling kit(s), what technique have you utilized for placement?
Q8	If you have utilized a trans-obturator polypropylene mesh midurethral sling kit(s), what technique have you utilized for placement?
Q9	Have you ever read the Instructions for Use manual on a polypropylene mesh midurethral sling kit?
Q10	If you answered yes above, with what frequency have you read it?
Q11	If you answered “until comfortable” above, approximately how many mesh placements did you perform until comfortable?
Q12	Have you ever read the Instructions for Use manual on a polypropylene mesh prolapse kit?
Q13	If you answered yes above, with what frequency have you read it?
Q14	If you answered “until comfortable” above, approximately how many mesh placements did you perform until comfortable?





Key of Definitions

IFU=Instructions for Use

FPMRS=Female Pelvic Medicine and Reconstructive Surgery